AMENDMENTS TO THE SPECIFICATION

The paragraph citations below refer to the corresponding paragraphs of the substitute specification filed on May 15, 2002.

Please replace the title, in its entirety, at page 1, lines 2-3, with the following rewritten title:

~~Genetic Sequences and Proteins Related to Alzheimer's Disease~~ Antibody Specific for Presenilin 1 and Method of Use Thereof

Please replace the paragraph at page 1, lines 5-9, with the following rewritten paragraph:

D1

This application is a divisional of U.S. Patent Application Serial No. 08/509,359, filed on July 13, 1995, Continuation-in-Part of U.S. Application Serial No. 08/496,841, filed on June 28, 1995, now Patent No. 6,210,919, which is a Continuation-in-Part of U.S. Application Serial No. 08/431,048, filed on April 28, 1995, now Patent No. 6,531,586.

Please replace the paragraph at page 6, lines 12-23, with the following rewritten paragraph:

D2

In accordance with another aspect of the invention, purified mammalian

Alzheimer's related membrane protein is provided. The purified protein has an amino acid sequence encoded by polynucleotide sequence as identified above for which human is SEQ ID NO: 2 and SEQ ID NO: 134 (derived from another clone). The mouse amino acid sequence is defined by SEQ ID NO: ~~2~~ 4 and SEQ ID NO: 136, the latter being translated from another clone containing the entire coding region. The purified protein may have substitution mutations selected from the group consisting of positions identified in SEQ ID NO: 2 and Sequence ID NO: 134.

D2

Please replace the paragraph at page 11, lines 4-11, with the following rewritten paragraph:

Figure 2(a). Automated fluorescent chromatograms representing the change in nucleic acids which direct (by the codon) the amino acid sequence of the gene; Met 146 Leu.

D3

Figure 2(b). Automated fluorescent chromatograms representing the change in nucleic acids which direct (by the codon) the amino acid sequence of the gene; His 163 Arg.

Figure 2(c). Automated fluorescent chromatograms representing the change in nucleic acids which direct (by the codon) the amino acid sequence of the gene; Ala 246 Glu.

Figure 2(d). Automated fluorescent chromatograms representing the

change in nucleic acids which direct (by the codon) the amino acid sequence of the gene; Leu 286 Val.

Figure 2[e]. Automated fluorescent chromatograms representing the change in nucleic acids which direct (by the codon) the amino acid sequence of the gene; Cys 410 Tyr.

D3 cont

Please delete in its entirety the paragraph at page 11, lines 12-14:

~~Figure 3(a). Restriction of fragments of M 146 L mutation using BsphI restriction enzyme in AD patients. Absence of a restriction site indicates a mutant allele.~~

~~Please~~ delete in its entirety the paragraph at page 11, lines 15-17:

~~Figure 3(b). Presence of the His 163 Arg mutation detected by NlaIII restriction digestion. Absence of a restriction indicates a mutant allele.~~

~~Please~~ delete in its entirety the paragraph at page 11, lines 18-20:

~~Figure 3 (c). Presence of the Ala 246 Glu mutation in AD patients using DdeI restriction enzyme. Presence of the mutant allele leads to restriction.~~

Please delete in its entirety the paragraph at page 11, lines 21-23:

~~Figure 3 (d). Presence of the Cys 410 Tyr mutation in AD patients as assayed using allele specific oligonucleotides.~~

Please delete in its entirety the paragraph at page 11, lines 24-25:

~~Figure 3 (e). Presence of the Leu 286 Val mutation in AD patients using PvuII restriction enzyme in AD patients.~~

Please delete in its entirety the paragraph at page 11, lines 26-30:

~~Figure 4. RNA blot demonstrating the expression of ARMP protein mRNA in different regions of the brain including amygdala, caudate, corpus callosum, hippocampus, hypothalamus, substantia nigra, subthalamic nucleus and thalamus.~~

Please delete in its entirety the paragraph at page 12, lines 1-4:

~~Figure 5. RNA blot demonstrating the expression of ARMP protein mRNA in a variety of tissues including heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas.~~

Please replace the paragraph at page 12, lines 5-6, with the following rewritten paragraph:

D4

Figure ~~6~~ 3a. Hydropathy plot for the putative ARMP protein.

Please replace the paragraph at page 12, lines 7-15, with the following rewritten paragraph:

Figure ~~6~~ 3b. A model for the structural organization of the putative ARMP protein. Roman numerals depict the transmembrane domains. Putative glycolsylation sites are indicated as asterisks and most of the phosporylation sites are located on the same membrane face as the two acidic hydrophilic loops. The MAP kinase site is present at residue 114. FAD mutation sites are indicated by horizontal arrows.

D5

Please delete in its entirety the paragraph at page 12, lines 16-23:

~~Figure 7 shows transcription of the E5-1 gene, investigate by hybridization of the E5-1 cDNA to Northern blots of mRNA from multiple human brain regions (Panel A), and several peripheral tissues (Panel C). In brain, the E5-1 transcript is of a lower molecular weight and lesser abundance than the ARMP transcript (Panel B) hybridized to the same blot using identical conditions.~~

Please replace the paragraph at page 12, lines 24-25, with the following rewritten paragraph:

Figure ~~8~~ 4 shows the predicted structure of the E5-1 protein.

D6

Please replace the paragraph at page 26, lines 2-20, with the following rewritten paragraph:

Hybridization of the S182 clone to northern blots identified a transcript expressed widely in many areas of brain and peripheral tissues as a major 3.0 kb transcript and a minor transcript of 7.0 kb ~~(Figures 4 and 5)~~. Although the identity of the ~7.0 kb transcript is unclear, two observations suggest that the ~3.0 kb transcript represents an active product of the gene. Hybridization of the S182 clone to northern blots containing mRNA from a variety of murine tissues, including brain, only a single transcript identical in size to the ~ 3.0 kb human transcript. All of the longer cDNA clones recovered to date (2.6-2.8 kb), which include both 5' and 3' UTRs and which account for the ~ 3.0 kb band on the northern blot, have mapped exclusively to the same physical region of chromosome 14. From these experiments the ~ 7.0 kb transcript could represent either a rare alternatively spliced or polyadenylated isoform of the ~ 3.0 transcript or could represent another gene with homology to S182.

D7

Please replace the paragraph at page 31, lines 16-22, with the following rewritten paragraph:

Of all the nucleotide substitutions consegregated with the disease in their respective pedigrees ~~(Figures 3a to 3e)~~, none were seen in asymptomatic family members aged more than two standard deviations beyond the mean age of onset, and none were present on 284 chromosomes from unrelated neurologically normal subjects drawn from comparable ethnic origins.

D8

Please replace the paragraph at page 79, line 15 to page 81, line 4, with the following rewritten paragraph:

The CEPH Mega YAC and the RPCI PAC human total genomic DNA libraries were searched for clones containing genomic DNA fragments from the AD3 region of chromosome 14q24.3 using oligonucleotide probes for each of the ## SSR marker loci used in the genetic linkage studies as well as the ## additional markers depicted in Figure 1a (Albertsen et al., 1990; Chumakov et al., 1992; Ioannu et al., 1994). The genetic map distance between each marker are depicted above the contig, and are derived from published data (NIH/CEPH Collaborative Mapping Group, 1992; Weissenbach, J. et al., 1992; Gyapay, G. et al., 1994). Clones recovered for each of the initial marker loci were arranged into an ordered series of partially overlapping clones ("contig") using four independent methods. First, sequences

D9

representing the ends of the YAC insert were isolated by inverse PCR (Riley et al., 1990), and hybridized to Southern blot panels containing restriction digests of DNA from all of the YAC clones bearing overlapping sequences. Second, inter-Alu PCR was performed on each YAC, and the resultant band patterns were compared across the pool of recovered YAC clones in order to identify other clones bearing overlapping sequences (Bellamne-Chartelot et al., 1992; Chumalov et al., 1992). Third, to improve the specificity of the Alu-PCR fingerprinting, we restricted the YAC DNA with HaeIII or RsaI, amplified the restriction products with both Alu and LIH consensus primers, and resolved the products by polyacrylamide gel electrophoresis. Finally, as additional STSs were generated during the search for transcribed sequences, these STSs were also used to identify overlaps. The resultant contig was complete except for a single discontinuity between YAC932C7 bearing *D14S53* and YAC746B4 containing *D14S61*. The physical map order of the STSs within the contig was largely in accordance with the genetic linkage map for this region (NIH/CEPH Collaborative Mapping Group, 1992; Wang, Z., Webber, J.L., 1992; Weissenbach, J. et al., 1992; Gyapay, G. et al., 1994). However, as with the genetic maps, we were unable to unambiguously resolve the relative order of the loci withing the *D14S43/D14S71* cluster and the *D14S76/D14S273* cluster. PAC1 clones suggest that D14S277 is telomeric to D14S28, whereas genetic maps have suggested the reverse order. Furthermore, a few STS probes failed to detect hybridization patterns

in at least one YAC clone which, on the basis of the most parsimonious consensus physical map and from the genetic map, would have been predicted to contain that STS. For instance, the D14S268 (AFM265) and RSCAT7 STSs are absent from YAC788H12 ~~(Figure 3)~~. Because these results were reproducible, and occurred with several different STS markers, these results most likely reflect the presence of small interstitial deletion with one of the YAC clones.